5.2a Strategies to Optimize Delivery and Minimize Risks of EN: Motility Agents

Question: Does the routine use of motility agents improve clinical outcomes in critically ill patients?

Summary of Evidence: There were 16 studies, (5 level 1 and 11 level 2) that compared motility agents to a placebo, standard of care, other motility agents or as a mono vs. combined approach. Of these, 8 studies looked at the use of a single motility agent compared to placebo (1 level 1 study, 7 level 2 studies) and one compared the motility agent to none (1 level 2 study). Three of these studies compared erythromycin to placebo (Chapman 2000, Berne 2002, Reigner 2002, Makkar 2016), two compared metoclopramide to placebo (Yavagal 2000 and Nursal 2007, Makkar 2016), two compared a novel phase II motility agent, one compared camicinal to placebo (Deane 2018), one compared the use of enteral naloxone to placebo (Meissner 2003) while one compared a higher dose of a traditional Japanese herbal medication to a standard dose and to none (Doi 2020). The Makkar 2016 trial included 3 groups: erythromycin vs. metoclopramide vs. placebo as did the Baradari 2017 study that compared neostigmine to metoclopramide to a combined approach. Given the uncertainty around the safety and efficacy of naloxone as a motility agent, the data from the Meissner 2003 study was not included. Five studies conducted a head to head comparison of motility agents but the data from these studies was not included in a meta-analysis as the interventions varied (MacLaren 2008 erythromycin vs. metoclopramide; Baradari 2016 & 2017 neostigmine vs. metoclopramide; Heyland 2019 Ulimorelin vs. metoclopramide; Chapman 2020 TAK-954 (Selective 5-HT4 receptor agonist) vs. metoclopramide). Three studies (Nguyen 2007, Baradari 2017 and Charoensareerat 2020) compared combined vs. monotherapy. Boivin 2001, which was included in the 2015 CPGs, was moved to section 5.2b (motility agents vs. intestinal feeds) in the 2018 update.

Mortality: When the data from the seven studies of a single motility agent compared to placebo/control that reported on mortality were aggregated, the use of motility agents had no effect on mortality (RR 1.06, 95% CI 0.87, 1.28, p=0.56, test for heterogeneity I^2=0%; figure 1). Note that these results are with the Makkar 2016 group that received erythromycin, but similar results are seen if the metoclopramide group is analyzed instead (RR 1.07, 95% CI 0.88, 1.29, p=0.50, test for heterogeneity I^2=0%; figure not shown). In the Doi 2020 study , the mortality data from both high dose and low dose intervention groups were combined.

Infections: In the one study using naloxone, there was a significant reduction in pneumonia (Meissner 2003) and in the other study, metoclopramide had no effect on the incidence of pneumonia (Yavagal 2000). The time to development of pneumonia was statistically different in the one study (Yavagal) (5.95 days versus 4.46 days, p=0.006), however, the clinical significance of this difference is negligible. One study reported on the number of infections per group rather than the number of patients with infections and again there were no differences between the groups receiving erythromycin vs. placebo (Berne 2002). Rates of ICU acquired/ventilator associated pneumonia were no different between the groups receiving Ulimorelin vs. metoclopramide (Heyland 2019) or those receiving combination metoclopramide and erythromycin vs. metoclopramide alone (Charoensareerat 2020).

LOS, Ventilator days: There were no differences between the groups in the 9 studies that reported on these outcomes (Meissner 2003, Nursal 2007, Nguyen 2007, Makkar 2016, Baradari 2017, Deane 2018, Heyland 2019, Doi 2020), with the exception of Baradari 2016 who found a trend in the reduction of ICU LOS in their study of neostigmine vs. metoclopramide.

Other: Nutritional outcomes and markers of enteral feeding intolerance were reported in all trials but the heterogeneity of how these outcomes were reported precludes formal statistical aggregation. In the controlled trials, three found significant improvements or strong trends towards improvements in feeding success or reduced feeding tolerance in the motility agent group (Chapman 2000, Reignier 2002, Berne 2002, Meissner 2003), three studies found no significant difference but numerically, better outcomes were observed in these underpowered trials (Makkar 2016, Deane 2018, Doi 2020), whereas one trial (Nursal 2007) showed better outcomes in the control group but results were not statistically significant in this small trial of 19 patients. In the head-to-head comparisons, based on one trial evaluating erythromycin and metoclopramide, nutritional and enteral feeding intolerance outcomes improved in both groups compared to baseline and there were no differences between groups (MacLaren 2008). When considering trials of combination vs. monotherapy, there are mixed results when considering the impact on nutritional or enteral feeding intolerance outcomes.

Conclusion:

1) Motility agents have no effect on mortality, infectious complications, LOS or ventilation duration in critically ill patients.
2) Motility agents may improve nutritional intake and/or reduce enteral feeding intolerance.

***Level 1 study**: if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.*
***Level 2 study**: If any one of the above characteristics are unfulfilled.*

Table 1. Randomized Studies Motility Agents in Critically Ill Patients

Study	Population	Methods (score)	Intervention	Mortality # (%)† Experimental	Mortality # (%)† Control	Infections # (%)‡ Experimental	Infections # (%)‡ Control	Nutritional Indices Experimental	Nutritional Indices Control
Placebo-controlled Trials									
1) Chapman 2000	Mixed ICU patient with GRV>250ml N=20	C.Random: Yes ITT: yes Blinding: Yes (12)	Erythro 200 mg IV vs. placebo x 1 dose	NR	NR	NR	NR	**Successful feeding defined as GRV <250 mo and continuing with feeds.** Erythro 9/10 vs. placebo 5/10, p=0.05	
2) Yavagal 2000	Mixed ICU N=305	C.Random: not sure ITT: yes Blinding: yes (10)	Metoclopramide 10 mg NG q 6 h vs. placebo	73/ 131 (56)	92/174 (53)	**Pneumonia** 22/131 (17)	**Pneumonia** 24/174 (14)	NR	
3) Berne 2002	Critically injured patients n=48	C.Random: not sure ITT: no Blinding: no (6)	Erythromycin 250 mg IV q 6 hrs vs. placebo	2/32 (6)	2/36 (6)	**Pneumonia** 13/32 per group*	**Pneumonia** 18/36 per group*	**Feeds tolerated at 48 hrs** 58% 44 %; p=0.001 **Feeds tolerated for the study** 65% 59%; p=0.06	
4) Reignier 2002	Mixed ICU patients N=48	C.Random: not sure ITT: yes Blinding: no (6)	Erythro 250 mg q 6h IV vs. placebo x 5 days	6/20 (30)	8/20 (40)	NR	NR	**EN discontinued if GRV>250 or vomited:** Erythro 35% vs. Placebo 70%; p<0.001	
5) Meissner 2003**	ICU patients N=84	C.Random: yes ITT: no Blinding: double (11)	Naloxone 8 mg q 6 hrs via NG vs.. placebo	6/38 (16)	7/43 (16)	**Pneumonia** 13/38 (34)	**Pneumonia** 24/43 (56)	**Feeding volumes after day 3** Higher in naloxone group (trend) **Amount of Reflux (mls)** 54 129	
6) Nursal 2007	Traumatic Brain Injured patients N=19	C.Random: no ITT: no Blinding: double (10)	Metoclopramide 10 mg IV TID vs. saline IV TID	**Hospital** 3/10 (30)	**Hospital** 3/9 (33)	NR	NR	**Patients with high GRV** 5/10 (50) 2/9 (22); p=0.22 **Days to target calories** 5.8 ± 5.2 3.5 ± 1.4; p=0.23 **Calorie intake/total calories** 61.3 ± 35.5% 92.2 ± 8.0 %; p=0.04	

7) Makkar 2016	Trauma pts with TBI, GCS >5 N=122	C.Random: yes ITT: no Blinding: double (8)	Erythromycin 250 mg tablet for 5 days vs. Metoclopramide 10 mg tablet for 5 days vs. placebo (vitamin C) for 5 days	**Erythromycin** **Unknown type** 4/38 **Metoclopramide** **Unknown type** 6/39	**Unknown type** 3/38; p=0.574	NR	NR	**Number of patients with high GRVs** **erythro.** **metocl.** **Control** 11/38 17/39 23/38 p=0.30 **Feeding failures (2 consecutive high GRVs)** 6/38 10/39 11/38 p=NS
8) Deane 2018	ICU patients on vasopressors or ISS ≥ 15 or GCS ≤12 or high dose opioids N=84	C.Random: yes ITT: no Blinding: double (11)	Camicinal (GSK) 50 mg given enterally vs. 10 ml enteral placebo. EN as per standard practice in both groups.	**All cause** 11/42 (26)	**All cause** 7/38 (18)	NR	NR	**Avg % goal volume delivered via EN** 77% [71, 83] 68% [58, 78], p=NS **% pts receiving ≥ 80% goal** 67% 74% **Incidence of feed intolerance** 15% 14%
9) Doi 2019	Critically ill requiring gastric feeding for ≥ 5 days N=26	C.Random: no ITT: no Blinding: no (5)	Rikkunshito (traditional Japanese herbal medicine) high dose 5 gm TID vs. Rikkunshito standard dose 2.5 mg TID vs. None (no placebo) for 5 days	**ICU** 3/17 (17.6%)ǂ **Hospital** 3/17 (17.6%)ǂ	**ICU** **1/9 (11)** **Hospital** **1/9 (11%)**	NR	NR	**Rikkunshito high dose vs. standard dose vs. none** **GRVs ≥ 300 mL/day, n (%)** 1/9 (11) vs. 1/8 (13) vs. 2/9 (22); p=1.00 **Diarrhea, n (%)** 2/9 (22) vs. 2/8 (25) vs.1/9 (11); p=0.84 **Vomiting, n (%)** None in all groups **Day 5 % EN target reached, median,** 62% (IQR 17–83%) vs. 40% (IQR, 26–61%) vs. 59% (IQR 39–63%); p=0.42
Head to Head Comparisons								
10) MacLaren 2008	Mixed ICU patient with GRV>150ml N=20	C.Random: not sure ITT: yes Blinding: no (9)	Erythromycin 250 mg q6h vs. Metoclopramide 10 mg IV q 6h for 4 doses	NR	NR	NR	NR	**Both agents resulted in significant reduction in GRV and increase in feeding rate** **Erythromycin vs. Metoclopramide** **GRV mL after dose 4** (mean SD) 36 ±48 (p<0.01 from baseline) vs. 21±23 (p<0.05 from baseline) **Feeding rate mL/hr after dose 4** (mean SD) **45** ± 21 (p<0.05 from baseline) vs. 44 ± 22 (p<0.05 from baseline) **% patients achieved goal feeding** 4/10 (40%) vs. 3/10 (30%) **Diarrhea** 3/10 (30%) vs. 1/10 (10%)

11) Baradari 2016	Mechanically ventilated ICU patients with NG in place and GRX >120 ml 3h after last gavage N=60	C.Random: yes ITT: no Blinding: double (6)	Neostigmine 2.5 mg IV at baseline and 6h later vs. metoclopramide 10 mg at baseline and 6h later. EN in both groups given as bolus – feeds of 180 ml every 3h.	**Neostigmine Unknown type** 1/30	**Metoclopramide Unknown type** 2/30	NR	NR	**Median time from intervention to GRV improvement** **Nestigmine** **Metoclopramide** 6h (CI 3.75-8.25) 9h (CI 7.38-10.17) p=NS **Adverse affects** 20.4% 7.2% **Diarrhea** 2 (6.8%) 0
12a) Baradari 2017	EN fed mechanically ventilated ICU patients with GRVs >120 ml 3h after last gavage N=90	C.Random: yes ITT: yes Blinding: double (10)	Neostigmine 2.5 mg IV vs. metoclopramide 20mg IV given over 60 minutes after enrollment. Standard EN for all groups: 250 ml EN every 4h. *Combo group shown in table below as 12b*	**Neostigmine Unknown type** 1/30	**Metoclopramide Unknown type** 2/30	NR	NR	**Median time from intervention to GRV improvement** **Nestigmine** **Metoclopramide** 3h (CI 2.9-4.99) 6h (CI 4.83-7.17) **Adverse affects** 16.7% 3.3%
13) Heyland 2019	Mechanically ventilated, intolerant to gastric tube feedings (GRV ≥ 500ml) (multicenter) N=120	C.Random: yes ITT: no Blinding: double (9)	Ulimorelin 600µg/kg in 50ml IV infusion vs. Metoclopramide 10mg in 50ml IV infusion. Both given for 30 mins, 8 hourly	**Ulimorelin 5 day** 5/62 (6.5%) **30 day** 19/62 (30.6%) **Due to adverse events** 3/62 (4.8%)	**Metoclopramide 5 day** 1/58 (1.7%) **30 day** 15/58 (25.9%) **Due to adverse events** 1/58 (1.7%)	**Ulimorelin ICU-acquired pneumonia** 11/62 (17.7%)	**Metoclopramide ICU-acquired pneumonia** **11/58 (19%)**	**Day 1-5** **% daily protein target rate achieved, mean, IQR** 82.9 (38.4,110.2) 82.3 (65.6, 11.2); p=0.49 **Feeding success, n(%)** 32 (51.6) 32 (55.2) **GRV > 500ml, n(%)** 31 (50) 33 (56.9) **Vomiting or regurgitation, n(%)** 14 (22.6) 10 (17.2) **Tracheal aspirate positive for pepsin, n(%)** 21 (33.9) 18 (31.0) **Constipation, n(%)** 2 (3.2) 0 (6.9)
14) Chapman 2020	Mechanically ventilated patients with enteral feeding intolerance (GRV>200ml) N=13	C.Random: yes ITT: yes Blinding: double (12)	TAK-954 (Selective5-HT4 receptor agonist) 0.5mg single dose IV over 1 hour and 0.9% NaCl QID vs. 0.9% NaCl single dose IV over 1 hour and Metoclopramide 10mg QID IV	**TAK-954** 2/7 (29%)	**Metoclopramide** 3/6 (50%)	NR	**NR**	**4 hr GRV, ml, median (min,max)** 0(0,24) 5.5 (0, 65) **10 hr GRV, ml, median (min,max)** 20 (0,150) 27.5 (0, 160) **16 GRV, ml, median (min,max)** 15 (0, 60) 10 (0,140) **22h GRV ml, median (min,max)** **10 (0,300)** **30 (0,420)**

Combo vs. Mono								
15) Nguyen 2007	Mixed ICU patients N=75	C.Random: yes ITT: yes Blinding: double (11)	Combination of Erythromycin 200 mg IV bid + Metoclopramide 10 mg IV qid vs. Erythromycin 200 mg IV bid alone	**Combo** **Hospital** 8/37 (22%)	**Mono** **Hospital** 10/38 (26%)	NR	**NR**	**Failure of feeding (days)** 6.5 ± 0.5 4.5 ± 0.5 **Caloric intake % prescribed 7 days** Higher in combination group (p=0.02) **Gastric residual volumes** Lower in combination group (p<0.05) **Need for post-pyloric feeds** 2/37 (5) 8/38 (21)
12b) Baradari 2017	*As above*	*As above*	*In addition to head to head comparison:* Combination of neostigmine 2.5 mg + metoclopramide 20 mg given over 60 minutes after enrollment	**Combo** **Unknown type** 1/30	*As above*	NR	NR	**Median time from intervention to GRV improvement, combo group** 3h (CI 2.01-3.3) **Adverse affects, combo group** **10%**
16) Charoensareerat 2020	Mechanically venilated,critically ill patients with enteral feeding intolerance N=35	C.Random: yes ITT: yes Blinding: double (13)	Metoclopramide 10mg IV every 6-8hrs (total 40mg) + erythromycin 250mg enterally vs. metoclopramide plus placebo every 6 hrs for 7 days	**Hospital** 11/17 (64.7%) **28 day** 10/17 (58.8%)	**Hospital** 12/18 (66.7%); p=1.00 **28 day** 12/18 (66.7%); p=0.73	**VAP** 1/17 (5.9%)	**VAP** 0/18 (0%); p=0.46	**Rate of successful feeding, n(%)** 8 (47.1) 11 (61.1); p=0.51 **Time to achieve successful feeding, median (IQR), h** 44 (20-68) 44 (16-96); p=0.97 **Average GRV, ml/d Day 1** 377.5 ± 396.4 414.3 ± 326.2; p=0.77 **Average GRV, ml/d Day 7** 149.2 ± 92.8 227.5 ± 275.6; p=0.53

* infections reported as per group, not # patients with infections
**data from this study not included in the meta-analysis due to the uncertainty around the safety and efficacy of naloxone as a motility agent.
ǂ mortality data from both interventional groups in this study (higher and standard doses) were combined

Table 1. Randomized Studies Motility Agents in Critically Ill Patients (continued)

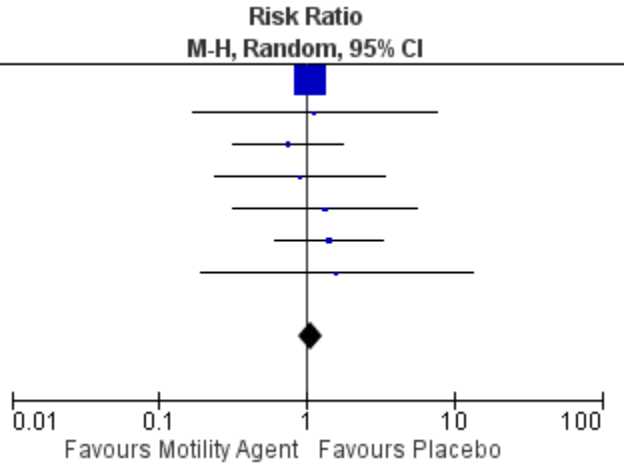
Study	ICU LOS		Hospital LOS		Mechanical Ventilation	
	Experimental	Control	Experimental	Control	Experimental	Control
Placebo-controlled Trials						
1) Chapman 2000	NR	NR	NR	NR	NR	NR
2) Yavagal 2000	NR	NR	NR	NR	NR	NR
3) Berne 2002	NR	NR	NR	NR	NR	NR
4) Reignier 2002	NR	NR	NR	NR	NR	NR
5) Meissner 2003**	17.5 (11-26) P=0.61	19 (13.5-24)	24 (16-33) P=0.92	23 (14-34)	11.5 (7-20.5) P=0.35	13 (10-20)
6) Nursal 2007	16.8 ± 8.5 P=0.819	15.6 ± 11.1	NR	NR	NR	NR
7) Makkar 2016	**Erythromycin** 8.5 ± 3.59 **Metoclopramide** 8.9 ± 4.99; p=0.275	10.4 ± 7.17	NR	NR	**Erythromycin** 7.14 ± 3.23 **Metoclopramide** 7.85 ± 4.93; p=0.295	8.97 ± 7.1
8) Deane 2018	Mean and SE 14 ± 1	Mean and SE 12 ± 2; p-value NR	Mean and SE 27 ± 3; p-value NR	Mean and SE 24 ± 3	Mean and SE 11 ± 2	Mean and SE 8 ± 1; p-value NR
9) Doi 2019	**Rikkunshito high dose** 5(4-14) **. Rikkunshito standard dose** 6(3-8)	7 (4-9); p=0.92	**Rikkunshito high dose** 42 (26-48) **Rikkunshito standard dose** 35 (30-40)	56 (35-82); p=0.19	NR	NR

Head to Head Comparisons						
10) MacLaren 2008	NR	NR	NR	NR	NR	NR
11) Baradari 2016	**Neostigmine** 20 (16-20)	**Metoclopramide** 17.5 (13-20); p=0.072	NR	NR	**Neostigmine** 12 (6.5-15)	**Metoclopramide** 11.5 (7-13); p=0.58
12a) Baradari 2017	**Neostigmine** 18.97 ± 6.25	**Metoclopramide** 16.8 ± 6.27; p=0.4	NR	NR	**Neostigmine** 12.17 ± 4.56	**Metoclopramide** 11.13 ± 3.84; p=0.71
13) Heyland 2019	**Ulimorelin** 14.9 (10.8, 20.8)	**Metoclopramide** 14.7 (11.8, 22.0)	**Ulimorelin** 33.7 (25.0, 43.8)	**Metoclopramide** 25.8 (18.1, 35.0)	**Ventilator Free days** 15.9 (0.0, 24.5) 15.5 (0.0, 23.3)	
14) Chapman 2020	NR	NR	NR	NR	NR	
Combo vs. Mono						
15) Nguyen 2007	NR	NR	**Combo** 53.0 ± 6.1	**Mono** 47.8 ± 9.1; p=NS	NR	NR
12b) Baradari 2017	**Combo** 18.27 ± 6.3	*As above*	NR	NR	**Combo** 11.8 ± 5.91	***As above***
16) Charoensareerat 2020	NR	NR	13 (1-68)	11.5 (1-62); p=0.57	NR	NR

Figure 1. Mortality*

Study or Subgroup	Motility Agent Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Yavagal	73	131	92	174	84.3%	1.05 [0.86, 1.30]	2000
Berne	2	32	2	36	1.0%	1.13 [0.17, 7.53]	2002
Reignier	6	20	8	20	4.9%	0.75 [0.32, 1.77]	2002
Nursal	3	10	3	9	2.1%	0.90 [0.24, 3.38]	2007
Makkar	4	38	3	38	1.8%	1.33 [0.32, 5.56]	2016
Deane	11	42	7	38	5.1%	1.42 [0.61, 3.29]	2018
Doi	3	17	1	9	0.8%	1.59 [0.19, 13.15]	2020
Total (95% CI)		**290**		**324**	**100.0%**	**1.06 [0.87, 1.28]**	
Total events	102		116				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.41$, df = 6 (P = 0.97); $I^2 = 0\%$
Test for overall effect: Z = 0.58 (P = 0.56)



*Showing data for erythromycin motility agent group in Makkar study

References

Included Studies

1. Chapman MJ, Fraser RJ, Kluger MT, Buist MD, De Nichilo DJ. Erythromycin improves gastric emptying in critically ill patients intolerant of nasogastric feeding. Crit Care Med. 2000 Jul;28(7):2334-7. Comment in: Crit Care Med. 2000 Jul;28(7):2657-9.
2. Yavagal DR, Karnad DR, Oak JL: Metoclopramide for preventing pneumonia in critically ill patients receiving enteral tube feeding: A randomized controlled trial. Crit Care Med 2000;May;28(5):1408-11.
3. Berne JD, Norwood SH, McAuley CE, Vallina VL, Villareal D, Weston J, McClarty J. Erythromycin reduces delayed gastric emptying in critically ill trauma patients: a randomized, controlled trial. J Trauma. 2002 Sep; 53(3): 422-5.
4. Reignier J, Bensaid S, Perrin-Gachadoat D, Burdin M, Boiteau R, Tenaillon A.Erythromycin and early enteral nutrition in mechanically ventilated patients. Crit Care Med 2002;Jun; 30(6): 1237-41.
5. Meissner W, Dohrn B, Reinhart K. Enteral naloxone reduces gastric tube reflux and frequency of pneumonia in critical care patients during opioid analgesia. Crit Care Med 2003 Mar; 31(3):776-80.
6. Nguyen NQ, Chapman M, Fraser RJ, Bryant LK, Burgstad C, Holloway RH. Prokinetic therapy for feed intolerance in critical illness: One drug or two? Crit Care Med 2007;35(11):2561-2567.
7. Nursal TZ, Erdogan B, Noyan T, Cekinmez M, Atalay B, Bilgin. The effect of metoclopramide on gastric emptying in traumatic brain injury. J Clin Neurosurg 2007;14:344-348.
8. MacLaren R, Kiser TH, Fish DN, Wischmeyer PE. Erythromycin vs metoclopramide for facilitating gastric emptying and tolerance to intragastric nutrition in critically ill patients. JPEN J Parenter Enteral Nutr 2008;32(4):412-419.
9. Makkar JK, Gauli B, Jain K, Jain D, Batra YK. Comparison of erythromycin versus metoclopramide for gastric feeding intolerance in patients with traumatic brain injury: A randomized double-blind study. Saudi J Anaesth. 2016 Jul-Sep;10(3):308-13. doi: 10.4103/1658-354X.174902. PubMed PMID: 27375386; PubMed Central PMCID: PMC4916815.
10. Gholipour Baradari A, Alipour A, Firouzian A, Moarab L, Emami Zeydi A. A Double-Blind Randomized Clinical Trial Comparing the Effect of Neostigmine and Metoclopramide on Gastric Residual Volume of Mechanically Ventilated ICU Patients. Acta Inform Med. 2016 Dec;24(6):385-389.
11. Baradari AG, Khajavi MR, Firouzian A, Alipour A, Daneshpour H, Panahi Y, Sahebkar A. Effects of combined prokinetic administration on gastric emptying in critically ill patients. Arab J Gastroenterol. 2017 Mar;18(1):30-34.

12. Deane AM, Lamontagne F, Dukes GE, Neil D, Vasist L, Barton ME, Hacquoil K, Ou X, Richards D, Stelfox HT, Mehta S, Day AG, Chapman MJ, Heyland DK. Nutrition Adequacy Therapeutic Enhancement in the Critically Ill: A Randomized Double-Blind, Placebo-Controlled Trial of the Motilin Receptor Agonist Camicinal (GSK962040): The NUTRIATE Study. JPEN J Parenter Enteral Nutr. 2018 Jul;42(5):949-959.
13. Chapman MJ, Jones KL, Almansa C, Barnes CN, Nguyen D, Deane AM. Blinded, Double-Dummy, Parallel-Group, Phase 2a Randomized Clinical Trial to Evaluate the Efficacy and Safety of a Highly Selective 5-Hydroxytryptamine Type 4 Receptor Agonist in Critically Ill Patients With Enteral Feeding Intolerance. JPEN J Parenter Enteral Nutr. 2020 Jan 28. doi: 10.1002/jpen.1732. Epub ahead of print. PMID: 31990087.
14. Heyland DK, van Zanten ARH, Grau-Carmona T, Evans D, Beishuizen A, Schouten J, Hoiting O, Bordejé ML, Krell K, Klein DJ, Gonzalez J, Perez A, Brown R, James J, Harris MS; Investigators of the PROMOTE LP101-CL-201 Trial. A multicenter, randomized, double-blind study of ulimorelin and metoclopramide in the treatment of critically ill patients with enteral feeding intolerance: PROMOTE trial. Intensive Care Med. 2019 May;45(5):647-656. doi: 10.1007/s00134-019-05593-2. Epub 2019 May 6. PMID: 31062046.
15. Charoensareerat T, Bhurayanontachai R, Sitaruno S, Navasakulpong A, Boonpeng A, Lerkiatbundit S, Pattharachayakul S. Efficacy and Safety of Enteral Erythromycin Estolate in Combination With Intravenous Metoclopramide vs Intravenous Metoclopramide Monotherapy in Mechanically Ventilated Patients With Enteral Feeding Intolerance: A Randomized, Double-Blind, Controlled Pilot Study. JPEN J Parenter Enteral Nutr. 2020 Sep 7. doi: 10.1002/jpen.2013. Epub ahead of print. PMID: 32895971.
16. Doi M, Miyamoto K, Shimokawa T, Ariyasu H, Kaneko M, Yonemitsu T, Nakashima T, Matsumoto H, Shibata M, Shibata N, Soda M, Kitaichi K, Kato S. The effect of standard and high dose of rikkunshito on achievement of enteral nutrition target in critically ill patients: a pilot randomized controlled trial. Acute Med Surg. 2019 Jul 9;7(1):e442. doi: 10.1002/ams2.442. PMID: 31988757; PMCID: PMC6971452.

Excluded Studies

1. Dive A, Miesse C, Galanti L, Jamart J, Evrard P, Gonzalez M, Installe E. Effect of erythromycin on gastric motility in mechanically ventilated critically ill patients : A double-blind, randomized, placebo-controlled study. Crit Care Med 1995;23(8):1356-1362.	Crossover design
2. Spapen HD, Duinslaeger L, Diltoer M, Gillet R, Bossuyt A, Huyghens L. Gastric emptying in critically ill patients is accelerated by adding cisapride to a standard enteral feeding protocol: Results of a prospective, randomized, controlled trial. Crit Care Med 1995;23(3):481-485.	Cisapride
3. Heyland DK, Tougas G, Cook DJ, Guyatt GH. Cisapride improves gastric emptying in mechanically ventilated, critically ill patients. Am J Respir Crit Care Med 1996;154:1678-1683.	No clinical outcomes
4. Williams A. The effect of cisapride on gastric stasis in intensive care patients. Br J Intensive Care 1996;6:186-193.	Cisapride

5. Altomare DF, Rubini D, Pilot MA, Farese S, Rubini G, Rinaldi M, Memeo V, D'Addabbo A. Oral erythromycin improves gastrointestinal motility and transit after subtotal but not total gastrectomy for cancer. Br J Surg 1997;84:1017-1021.	Not critically ill
6. Goldhill DR, Toner CC, Tarling MM, Baxter K, Withington PS, Whelpton R. Double-blind, randomized study of the effect of cisapride on gastric emptying in critically ill patients. Crit Care Med. 1997 Mar;25(3):447-51. Comment in: Crit Care Med. 1998 Jan;26(1):188-9.	Cisapride
7. Jooste CA, Mustoe J, Collee G. Metoclopramide improves gastric motility in critically ill patients. Intensive Care Med 1999;25:464-468.	No clinical outcomes
8. MacLaren R, Kuhl DA, Gervasio JM, Brown RO, Dickerson RN, Livingston TN, Swift K, Headley S, Kudsk KA, Lima JJ. Sequential single doses of cisapride, erythromycin, and metoclopramide in critically ill patients intolerant to enteral nutrition: A randomized, placebo-controlled, crossover study. Crit Care Med 2000;28(2):438-444.	Crossover design
9. van der Spoel JI, Oudemans-van Straaten HM, Stoutenbeek CP, Bosman RJ, Zandstra DF. Neostigmine resolves critical illness-related colonic ileus in intensive care patients with multiple organ failure--a prospective, double-blind, placebo-controlled trial. Intensive Care Med. 2001 May;27(5):822-7.	Neostigmine
10. Booth CM, Heyland DK, Paterson WG. Gastrointestinal promotility drugs in the critical care setting: A systematic review of the evidence. Crit Care Med 2002;Jul;30(7):1429-35.	Systematic review, individual studies looked at
11. Chapman M, Fraser R, de Beaux I, Creed S, Finnis M, Butler R, Cmielewski P, Zacharkis B, Davidson G. Cefazolin does not accelerate gastric emptying in the critically ill. Intensive Care Med 2003;29:1169-1172.	Crossover design
12. Griffith DP, McNally AT, Battey CH, Forte SS, Cacciatore AM, Szeszycki EE,Bergman GF, Furr CE, Murphy FB, Galloway JR, Ziegler TR. Intravenous erythromycin facilitates bedside placement of postpyloric feeding tubes in critically ill adults: a double-blind, randomized, placebo-controlled study. Crit Care Med 2003 Jan; 31(1):39-44.	No clinical outcomes
13. Marino LV, Kiratu EM, French S, Nathoo N. To determine the effect of metoclopramide on gastric emptying in severe head injuries: a prospective, randomized, controlled clinical trial. Br J Neurosurg 2003 Feb;17(1):24-8.	No clinical outcomes

14. Ritz MA, Chapman MJ, Fraser RJ, Finnis ME, Butler RN, Cmielewski P, Davidson GP, Rea D. Erythromycin dose of 70 mg accelerates gastric emptying as effectively as 200 mg in the critically ill. Intensive Care Med. 2005 Jul;31(7):949-54. Epub 2005 Jun 7.	No clinical outcomes
15. Sustić A, Zelić M, Protić A, Zupan Z, Simić O, Desa K. Metoclopramide improves gastric but not gallbladder emptying in cardiac surgery patients with early intragastric enteral feeding: randomized controlled trial. Croat Med J. 2005 Apr;46(2):239-44.	No clinical outcomes
16. Memis D, Inal MT, Temizoz O, Genchallac H, Ozdemir H, Sut N. The effect of celiac plexus block in critically ill patients intolerant of enteral nutrition: a randomized, placebo-controlled study. Anesth Analg. 2010 Apr 1;110(4):1071-5. Epub 2010 Jan 26. Retraction in: Shafer SL. Anesth Analg. 2010 Dec;111(6):1561. PubMed PMID: 20103540.	retracted due to plagiarism
17. Nassaji M, Ghorbani R, Frozeshfard M, Mesbahian F. Effect of metoclopramide on nosocomial pneumonia in patients with nasogastric feeding in the intensive care unit. East Mediterr Health J. 2010 Apr;16(4):371-4. PubMed PMID: 20795418.	Pseudo-randomized
18. van den Bosch S, Witteman E, Kho Y, Tan AC. Erythromycin to promote bedside placement of a self-propelled nasojejunal feeding tube in non-critically ill patients having pancreatitis: a randomized, double-blind, placebo-controlled study. Nutr Clin Pract. 2011 Apr;26(2):181-5. PubMed PMID: 21447772.	Non-critically ill patients
19. Luan R, Tang H, Zhai S, Zhu X. [Erythromycin for improving enteral nutrition tolerance in adult critical patients: a systematic review and meta-analysis]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2014 Jun;26(6):425-30.	Meta-analysis
20. Hu B, Ye H, Sun C, Zhang Y, Lao Z, Wu F, Liu Z, Huang L, Qu C, Xian L, Wu H, Jiao Y, Liu J, Cai J, Chen W, Nie Z, Liu Z, Chen C. Metoclopramide or domperidone improves post-pyloric placement of spiral nasojejunal tubes in critically ill patients: a prospective, multicenter, open-label, randomized, controlled clinical trial. Crit Care. 2015 Feb 13;19:61.	no clinically important outcomes
21. Li J, Gu Y, Zhou R. Rhubarb to Facilitate Placement of Nasojejunal Feeding Tubes in Patients in the Intensive Care Unit. Nutr Clin Pract. 2016 Feb;31(1):105-10. doi: 10.1177/0884533615608363. Epub 2015 Oct 12. PubMed PMID: 26459161.	not studying a motility drug
22. Chapman MJ, Deane AM, O'Connor SL, Nguyen NQ, Fraser RJ, Richards DB, Hacquoil KE, Vasist Johnson LS, Barton ME, Dukes GE. The effect of camicinal (GSK962040), a motilin agonist, on gastric emptying and glucose absorption in feed-intolerant critically ill patients: a randomized, blinded, placebo-controlled, clinical trial. Crit Care. 2016 Aug 1;20(1):232. doi: 10.1186/s13054-016-1420-4. PMID: 27476581; PMCID: PMC4967996.	No clinically important outcomes